

An identifiability problem in a state model for partly undetected chronic diseases

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Abstract

Recently, we proposed an state model (compartment model) to describe the progression of a chronic disease with an pre-clinical (“undiagnosed”) state before clinical diagnosis. It is an open question, if a sequence of cross-sectional studies with mortality follow-up is sufficient to estimate the true incidence rate of the disease, i.e. the incidence of the undiagnosed and diagnosed disease. In this note, we construct a counterexample and show that this cannot be achieved in general.

1 Introduction

1.1 Compartment model

Recently, we introduced a compartment model with a pre-clinical stage preceding the clinical stage [1]. The model involves calendar time t , and the different ages a of the subjects in the population. The transition rates between the states are denoted as in Figure 1.

Using the definition $N(t, a) = S(t, a) + U(t, a) + C(t, a)$ and setting

$$\begin{aligned} p_0(t, a) &= \frac{S(t, a)}{N(t, a)} \\ p_1(t, a) &= \frac{U(t, a)}{N(t, a)} \\ p_2(t, a) &= \frac{C(t, a)}{N(t, a)}, \end{aligned}$$

the compartment model in Figure 1 is governed by a system of partial differential equations (PDEs):

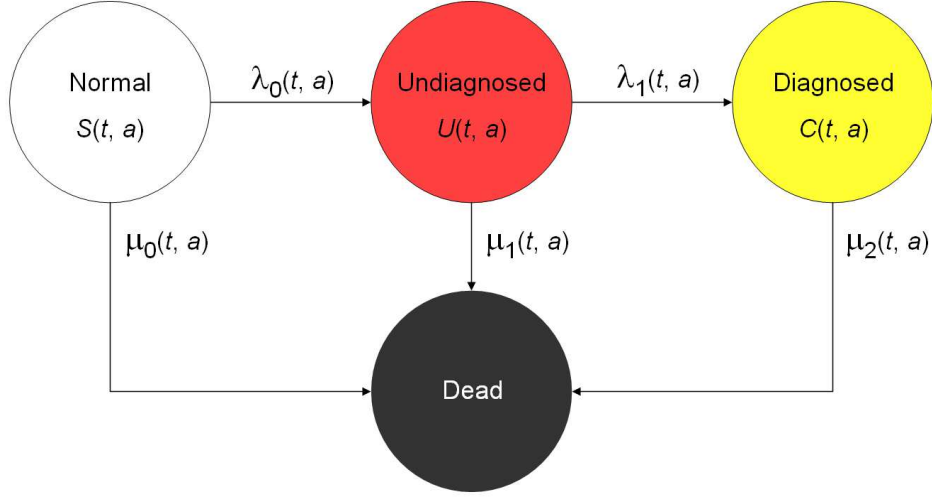


Figure 1: Chronic disease model with four states and the corresponding transition rates. People in the state *Normal* are healthy with respect to the disease under consideration. After onset of the disease, they change to state *Undiagnosed* and maybe later to the state *Diagnosed*. The absorbing state *Dead* can be reached from all other states. The numbers of persons in the states and the transition rates depend on calendar time t and age a .

$$\begin{aligned}
 (1) \quad & (\partial_t + \partial_a)p_1 = -(\lambda_0 + \lambda_1 + \mu_1 - \mu)p_1 - \lambda_0 p_2 + \lambda_0 \\
 (2) \quad & (\partial_t + \partial_a)p_2 = \lambda_1 p_1 - (\mu_2 - \mu)p_2.
 \end{aligned}$$

For brevity we have written $\partial_x = \frac{\partial}{\partial x}$, $x \in \{t, a\}$. In Eq. (1) – (2) the general mortality μ is given by

$$(3) \quad \mu = p_0\mu_0 + p_1\mu_1 + p_2\mu_2.$$

Together with the initial conditions $p_1(t, 0) = p_2(t, 0) = 0$ for all t , the system (1) – (2) completely describes the temporal dynamics of the disease in the considered population. The quantity p_0 can be obtained by

$$(4) \quad p_0 = 1 - p_1 - p_2.$$

1.2 Direct and inverse problem

Assumed that the functions $\lambda_0, \lambda_1, \mu_1, \mu_2, \mu$ on the right-hand sides of system (1) – (2) are sufficiently smooth, then the associated initial value problem

$p_1(t, 0) = p_2(t, 0) = 0$ for all t has a unique solution. This means that together with the initial condition, there is a function

$$(5) \quad \Phi : \Theta = (\lambda_0, \lambda_1, \mu_1, \mu_2, \mu) \mapsto P = (p_1, p_2).$$

Given the initial conditions, the operator Φ maps the transition rates Θ onto the uniquely associated prevalence functions $\Phi(\Theta) = P = (p_1, p_2)$. This problem is called the *direct problem* or *forward problem* [2].

Similar to the simpler compartment model in [3], the question arises if and under which circumstances the opposite way is possible. Does a series prevalence studies P allow to estimate the transition rates Θ ? Mathematically, this problem is expressed as inversion of the function Φ . Given P , the question is if there is a unique Θ such that $\Phi(\Theta) = P$? The problem of estimating the rates from prevalence data, is called an *inverse problem* [2]. It is not guaranteed that the inverse problem has a solution. Examination of conditions such that the inverse problem has a solution is called the analysis of *identifiability* [4].

Under certain circumstances, the operator Φ is indeed invertible. Assumed that the mortality rates μ_1, μ_2 , and μ are known, then for given $P = (p_1, p_2)$ the system (1) – (2) can be solved for λ_0 and λ_1 . Thus, in these cases Φ is invertible.

In the next section, we will show that is not always the case.

2 Identifiability problem

We consider two prevalence studies at calendar times $t_1 < t_2$ with *mortality follow-up*. This means, on the one hand we have estimates for the age courses of the prevalences p_1 and p_2 at t_1 and t_2 . On the other hand, we have additional information if and when any participant at t_1 has died before t_2 . Let us assume that for any participant who deceased between t_1 and t_2 , we do not have information about what state the person was in at the time of death. For example, a person who was in the *Normal* state at t_1 and died before t_2 could have deceased when he was still in the *Normal* state, in the *Undiagnosed* state or in the *Diagnosed* state. An exception is someone dying between t_1 and t_2 , who was in the *Diagnosed* state. As the *Diagnosed* state can only be left via the transition to *Dead* state, the information from the mortality follow-up helps to estimate μ_2 . Thus, the mortality follow-up contributes to estimate the general mortality μ or occasionally the mortality μ_2 , but not to estimate μ_0 or μ_1 .

The question arises: Given $p_k(t_j, \cdot)$, $j, k = 1, 2$, $\mu(t^*, \cdot)$ and $\mu_2(t^*, \cdot)$ for some t^* with $t_1 < t^* < t_2$, are we able to estimate the rates $\lambda_0, \lambda_1, \mu_0$, and μ_1 at

t^* ? In the following we will show that this is not the case. This is done by constructing a counterexample with given p_1, p_2, μ, μ_2 but different $\lambda_0, \lambda_1, \mu_0$, and μ_1 .

Consider the system (1) – (2) being in equilibrium such that $\partial_t p_k(t^*, a) = \partial_a p_k(t^*, a) = 0$, $k = 1, 2$, for all a . Furthermore, let $p_0 = 0.5, p_1 = 0.3$ and $p_2 = 0.2, \mu = 0.6, \mu_2 = 0.8$. Obviously, it holds $p_0 + p_1 + p_2 = 1$. From $\partial_x p_2 = 0$, $x \in \{t, a\}$ it follows that $\lambda_1 = (\mu_2 - \mu) \frac{p_2}{p_1} = \frac{4}{30}$. If we choose $\mu_1^{(1)} = 0.5$ and $\mu_1^{(2)} = 0.6$, then from $\mu = p_0 \mu_0 + p_1 \mu_1 + p_2 \mu_2$ it follows that $\mu_0^{(1)} = 0.58$ and $\mu_0^{(2)} = 0.52$. In addition, $\partial_x p_1 = 0$, $x \in \{t, a\}$ implies $\lambda_0 = (\lambda_1 + \mu_1 - \mu) \frac{p_1}{p_0}$. Thus, it holds $\lambda_0^{(1)} = 0.02$ and $\lambda_0^{(2)} = 0.08$. The results are summarized in Table 1.

Variable	Value 1	Value 2
p_0	0.5	
p_1	0.3	
p_2	0.2	
μ	0.6	
μ_2	0.8	
λ_1	$\frac{4}{30}$	
μ_1	0.5	0.6
μ_0	0.58	0.52
λ_0	0.02	0.08

Table 1: Example for non-identifiability of the system (1) – (4). In an equilibrium state ($\partial_x p_k = 0$, $k = 1, 2$, $x \in \{t, a\}$), measured values in the upper half of the table are consistent with the values in the lower half.

Hence, from given p_1, p_2, μ, μ_2 , in equilibrium, we were able to construct *different* $\lambda_0, \lambda_1, \mu_0$, and μ_1 , which are consistent with the system (1) – (4). This implies that two cross-sections at t_1 and t_2 with mortality follow-up are not sufficient to make the system identifiable.

3 Conclusion

In this technical note it was shown by a counterexample that two cross-sectional studies with mortality follow-up are not sufficient to make the system (1) – (4) identifiable. This means, from two cross-sectional studies and measured p_k , $k = 0, 1, 2$, and known μ, μ_2 it is not possible to estimate the incidence rates λ_0 and λ_1 .

The counterexample was constructed by the system (1) – (2) being in equilibrium. This is not a loss of generalizability. It is sufficient to find one example of non-identifiability to prove non-existence of a solution of the inverse problem.

Note that from measured p_k , $k = 0, 1, 2$, and known μ, μ_2 , the rate λ_1 is estimable. This can be seen by solving Eq. (2) for λ_1 .

References

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